Fiscal Year:	FY 2023	**Task Last Upd**	
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	david.goukassian@mssm.edu		
PI Organization Type:	UNIVERSITY	**P**	
Organization Name:	Icahn School of Medicine at Mount Sinai		
PI Address 1:	Zena & Michael A. Weiner Cardiovascular Institute		
PI Address 2:	One Gustave L. Levy Place, Box 1030		
PI Web Page:			
City:	New York		
Zip Code:	10029	**Congressional Di**	
Comments:	NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018.		
Project Type:	Ground	**Solicitation / Funding So**	
Start Date:	04/10/2019	**End**	
No. of Post Docs:	3	**No. of PhD Deg**	
No. of PhD Candidates:	2	**No. of Master' De**	
No. of Master's Candidates:	1	**No. of Bachelor's De**	
No. of Bachelor's Candidates:	1	**Monitoring Co**	
Contact Monitor:	Zawaski, Janice	**Contact P**	
Contact Email:	janice.zawaski@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome," grant 80NS NOTE: End date changed to 02/15/2024 per NSSC information (Ed., 5/26/23)		
Key Personnel Changes/Previous PI:	PI notes additional collaborators who are assisting with the project: Lahouaria Hadri, Kenneth Walsh, and Venkata Naga SrikanthGarikpati (Ed., 5		
COI Name (Institution):	Kishore, Raj (Temple University School of Medicine)		
Grant/Contract No.:	80NSSC19K1079		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	Ed. note 2/10/2020: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome." During the future Moon, near Earth asteroids, and Mars missions, astronauts will be exposed to higher total doses of space irradiation (IR) (~0.4-0 breast cancer has shown that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no apparen cancer treatment (1.25 Gy total-body irradiated), identified seven urine-based biomarkers with distinct differences between pre- and post-exposure Hypotheses: Our central hypothesis is that low-dose proton and HZE (high energy) particle IR-induced biological responses are long-lasting, IR ty effective (RBE) IR thresholds for CV risk estimates. Gene expression and epigenetic modifications in protein and microRNA (miRNA) in exosom AIM 1. Determine the longitudinal effect of IR type, dose, and sex on cardiovascular physiology in wild type mice and ApoE null mice after full-b AIM 2. Determine space-type IR mediated modulations in exosomal cargo in the blood, and determine whether these changes are associated with AIM 3. Utilize known and newly identified biomarkers in the blood to develop human-relevant point-of-care tests (POCT) for predicting and mon We anticipate that the results of our proposed work may be beneficial for human space exploration and could (1) Determine single whole body mi modifications in the circulating exosomal cargo contents and whether IR-induced exosomal cargo modulations are reflective of subclinical change data sets with gene expression and epigenetic data to identify biomarkers in bio-fluids that could be used for prediction of asymptomatic CVD in t		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	We anticipate that the results of our work could be beneficial for human space exploration as well as for the Earth-based applications on several le signaling of CV alterations; (3) identify biomarkers in the blood that could be used for prediction of asymptomatic CV disease, which will include treatment of IR-induced CVDs in space and in Earth-bound civilian population, in general.		
	Our new findings for the reporting period are organized below by four sub-titles containing corresponding background, methodology, main finding Sub-project 1: Title: "Lifetime Evaluation of Cardiac Function and Structure in C57bl/6j Mice after Gamma and Space-Type Radiation Exposure" Background. The lifetime effects of space irradiation (IR) on left ventricular (LV) function are unknown. The cardiac effects induced by space-typ whole-body IR exposure; (3) establish whether dose thresholds for gamma (γ) and simGCRsim IR exist; and (4) describe the comparative impact Methods. Three-month-old, age-matched, male C57BL/6J mice were irradiated with 137Cs gamma (gamma; 100, 200 cGy) and 5-ion simplified G We assessed the mRNA expression of genes involved in cardiac remodeling, fibrosis, inflammation, and calcium handling in LVs harvested at 66 Main Findings. All IR groups had impaired global LV systolic function at 14, 28, and, 365 days. At 660 days, 50 cGy simGCRsim-IR mice exhibi cardiac remodeling processes commonly associated with diastolic dysfunction. IR groups showing statistical significance were modeled to calcula Summary. Our work is the first to assess in mice the lifetime longitudinal effects of simGCRsim-IR at doses of 50 and 100 cGy and γ-IR at doses cGy) wild-type C57BL/6J male mice as early as 14 and 28 days post IR, as well as 365 and 440 days post–IR; (2) at 660 days post IR, simGCRsim expression of markers of cardiac fibrosis (TGFB1, MMP9), inflammation (MCP-1), and hypertrophy (βMHC), results that suggest simGCRsim-IR Sub-project 2: Title: "Lifetime Risk of Tumor Development in C57b1/6j Mice Exposed to a Single Full Body Gamma and C57B1/6J MICE EXPOSED TO A SI Background: Radiation-induced cancer is one of the primary risks associated with exposure to space radiation (IR) during deep-space missions. Th processes. Methods: As part of our NASA-funded mouse-lifetime studies to evaluate the effect of space-type and gamma (γ)-IR on cardiovascular disease (C 5-ion simplified GCR simulation-IR (simGCRsim). Control ApoE null and WT mice were fed with mouse chow (normal diet-ND) and one group pathologists blindfolded to treatment conditions. Main Findings: At all time points and treatment conditions examined, a total of 9 neoplasms were detected in ApoE null mice, including ND-fed n 7/17 (41%) animals developing neoplasms at 16 and 22 months, respectively. A small number of WD-fed and 100 cGy γ-IR mice developed more tumor prevalence represented by lymphoma, hemangiosarcoma, hepatoblastoma, early carcinoma (all liver) and hemangiosarcoma, lymphoma (sp in 50 cGy simGCRsim-IR WT mice. Lung tumors were not observed at 22 months in any treatment group, though hepatic and splenic tumors wer Summary: Our studies revealed that – i) the incidence of tumors is higher in WT compared to ApoE null mice after the same doses of γ- and simG IR-induced internal organ tumors was higher in 100 cGy γ- versus 50 cGy simGCRsim-IR, suggesting higher carcinogenic potential of γ-IR at the		

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SC18K0921, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University. (Ed., 2/10/2020)

/26/23).

grant 80NSSC18K0921 with the same Principal Investigator Dr. David Goukassian, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University.
5 Gy) from galactic cosmic rays (GCR). Most of what we know about harmful effects of IR on cardiovascular (CV) system is from epidemiological studies of long-term survivors of cancer radiotherapy (RT). A recent study of 2,168 women who underwent RT for nt lower or upper threshold. In this study, it was determined that average of the mean doses to the whole heart was 4.9 Gy with the range of 0.03 - 27.72 Gy. Furthermore, metabolomics studies, in patients undergoing hematopoietic stem cell (HSC) transplantation as part of samples. The levels of these markers were found to be sex-dependent suggesting that separate biomarker signatures may exist for males and females.

pe- and dose-dependent and may augment excess relative risk (ERR) estimates for the development of cardiovascular diseases (CVDs) during and after long-duration space missions. In addition, we hypothesize that sex differences could further modify radio-biologically es from the blood (e.g., plasma/serum) may be altered before the onset of the cardiac symptoms, which could be used as potential biomarkers to predict the CVD risks. We will test our hypotheses with the following specific aims:

ody 5-ion simplified mixed field and gamma radiation.

alterations in the heart function, structure, and vasculature before the manifestation of clinical symptoms.

itoring possible CV alterations before and during space flights.

xed field dose-response, radio-biologically effective IR thresholds in the heart and cardiac vasculature, and whether sex differences could modify radio-biologically effective IR thresholds for CV risk estimates; 2) Determine whether space radiation leads to s in the cells and organs of origin; 3) Ascertain if modulations of exosomal cargo may be representative of chronic oxidative stress and inflammation and could serve as early biomarkers of IR-induced CVD initiation and progression; 4) Integrate physiological CV endpoint he setting of space IR, which will include known early and intermediate biomarkers of cardiac damage, inflammation, and oxidative stress, as well as currently unknown novel radiation-associated cardiac biomarkers.

vels -- (1) determine whether low dose space-type and terrestrial IR may present an increased risk for CVD development during and after prolonged space missions, as well as after conventional and particle cancer radiotherapy; (2) determine the underlying molecular known early and intermediate biomarkers of cardiac damage, as well as currently unknown novel cardiac biomarkers; (4) the identification of sub-clinical CV disease biomarkers that could be used for monitoring the effectiveness of mitigating factors for prevention and

gs, and the summary.

e IR, specifically simplified galactic cosmic ray simulation (simGCRsim), are yet to be discovered. This study aimed to - (1) determine the effects of (terrestrial) and simGCRsim (space) IR on LV function; (2) identify disease spectrum and latency following single, of γ and simGCRsim IR by calculating Relative Biological Effectiveness (RBE) and Radiation Effects Ratio (RER).

CR simulation (simGCRsim; 50, 100 cGy). LV function was assessed by transthoracic echocardiography at 14, 28 days (early), and 365, 440, 660 (late) days post-IR. We measured endothelial function markers of brain natriuretic peptide in plasma at three late time points.) days post IR. RBE and RER estimates were calculated for LV ejection fraction and LV fractional shortening, on which IR had a statistically significant effect.

ted preserved LV systolic function with altered LV size and mass. At this time point, simGCRsim-IR mice had elevated levels of cardiac fibrosis, inflammation, and hypertrophy markers TGFß1, MCP1, MMP9, and ßMHC, suggesting that space-type IR may induce te the Relative Biological Effectiveness (RBE) and Radiation Effects Ratio (RER). The observed dose-response shape did not indicate a lower threshold at these IR doses.

of 100 and 200 cGy on LV function and structure using echocardiography, serum biomarkers, and cardiac tissue structure alterations. Our findings can be summarized as follows: - (1) LV systolic function is impaired in simGCRsim (50, 100 cGy) and γ-IR (100, 200 n-IR male mice appear to have developed a HFpEF cardiac phenotype, though diastolic dysfunction cannot be ruled out, while the cardiac function is recovered in γ-IR mice; (3) cardiac function alterations at 660 days post IR appear to be associated with increased may dynamically affect cardiac remodeling processes throughout a lifetime; and (4) no clear dose-response was observed.

NGLE FULL BODY GAMMA AND simGCRsim Radiation"

ere is limited data in humans and in animal models for high charge and energy (HZE)-induced carcinogenesis over the murine lifetime. We hypothesize that exposure to space-type IR may increase the risk of cancer development, especially in association with aging

VD) development, mice were examined for tumor development during scheduled tissue collections over 22 months post-IR. Three-month-old male ApoE null and C57B1/6J wild-type (WT) mice were exposed to 100 cGy of 137Cs γ-IR and 50 cGy, 500 MeV/nucleon of in each genotype was fed Western diet (WD) without IR. Note, all IR mice were fed with a ND for 22 months. All neoplasms were fully bisected with visibly unaffected tissue. Formalin-fixed tissues were submitted for routine H&E staining and evaluation by two

ice. Therefore, we focused our further studies only on WT mice. A single WT mouse developed a lymphoma in control No-IR mice at 22 months. In WT mice, the prevalence of neoplasms (liver, lung, spleen) was the highest in no-IR, WD-fed mice with 9/15 (60%) and than one distinct tumor. At 16 months, tumors in WD-fed mice were represented by 7 liver tumors (2 - hepatocellular carcinomas, 1 - hemangiosarcoma, 4 - metastatic lymphomas), 1 lung (lymphoma), and 1 spleen (hemangiosarcoma) tumors. In WT IR mice, higher leen) was found in 100 cGy γ-IR mice 2/16 (12.5%) and 8/16 (50%) at 16 and 22 months, respectively. At the same respective time points, there were 1/15 (6.7%) and 6/15 (40%) tumors represented by lymphoma, hepatocellular carcinoma, histiocytic sarcoma (all liver) e higher in all groups.

CRsim-IR suggesting underlying genotypic variance may attenuate pathways involved in tumorigenesis; ii) the highest number of tumors during the lifetime of WT mice was detected in the WD-fed group, but not in either of IR groups, iii) in WT mice, the incidence of se doses; iv) the liver is the most affected organ by tumor growth, followed by the spleen. These results suggest that age-related metabolic changes and IR-induced mutagenesis may drive carcinogenesis.

Task Progress:	Sub-project 3: Title: "Space Radiation Induced Clonal Hematopoiesis: Lifetime Disease Susceptibility Risks and Identification of Biomarkers" Background: Recent epidemiological studies have documented the prevalence of somatic mutations within the cells of the hematopoietic system ir (CHIP). The recent NASA Twin Study provided a detailed analysis of how prolonged, low-orbit space travel may contribute to genotoxic stress ar leukocytes collected 21-24 years ago from 14 relatively young astronauts who flew space Shuttle missions between 1998-2001 to assay, retrospect beyond Earth's geomagnetic field where there is increased exposure to high atomic number and high energy IR. Methodology: Of particular interest to the proposed studies are findings in our preliminary mouse lifespan space IR studies. As part of our NASA after 100 cGy, of gamma (γ)- and 50 cGy (500 MeV/n) of 5-ion simplified GCR simulation (simGCRsim)-IR. Both types of IR showed deleterio in non-IR mice at 16 months and none at 22 months. To study the effects of aging and IR on the development of malignancies (hematopoietic and frequency (VAF) > 0.1%, and annotation was performed using ANNOVAR and MuTect. Main Findings: At 22 months post-IR mWES analysis revealed a higher incidence (8%) of non-frameshift deletions in both IR groups compared t common for aging and are increased after space-type exposure. Interestingly, stop-gain mutations were increased due to aging (7%) and WD-fed n (hematopoietic and solid) and cardiovascular diseases. Comparing mutation-type versus cancer pathology revealed that hepatocellular carcinoma v IR type include - 1) NF-kB pathway, 2) WNT/beta-catenin signaling pathway, and 3) different mediators of cell cycle checkpoints. Additional stu Summary: While the impact of space travel on CHIP is completely unknown, it is reasonable to speculate that space IR in combination with other of individual susceptibility, predictive genetic biomarkers and development of mitigation strategies before and after future deep space exploration Sub-project 4: Title: "Lifetime Evaluation of Cardiac Function and Structure in Female C57bl/6j and Apoe Null Mice after Gamma and Space-Type Radiation Ex Background: Space radiation (IR) from Solar Particle Events (SPE) and Galactic Cosmic Rays, also known as high charge and energy (HZE) ioniz Apolipoprotein-E (ApoE) null and C57BL6/J wild type (WT) male mice exhibit reduced global systolic function at 14 and 28 days after exposure: showed significant cardiac dysfunction paired with structural alterations. To assess for any sex-specific effects following IR exposure, we hypothe Methods: Three-month-old female age-matched WT and ApoE null mice were irradiated with 137Cs-γ -IR (100 cGy, 0.662 MeV) and simGCRsir clearance of elevated plasma low-density lipoproteins (LDL) levels, however, WT mice do not develop atherosclerosis. We assessed left ventricul Main Finding: At 28 days post-IR, 50 cGy simGCRsim-IR ApoE null and WT mice exhibit reduced Left ventricular ejection fraction (LVEF) and WD-fed mice and two IR groups of both genotypes. However, in WT mice LV internal diameter (LVIDd), stroke volume (SV), and LV mass were 440-, and 580 days post-IR. Summary: Our lifetime longitudinal echocardiography findings showed minimal and not statistically significant radiation-associated alterations in after space and terrestrial IR over the lifetime of female mice. These findings do not exclude the possibility of increased acute or degenerative CV
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n healthy individuals. These acquired DNA mutations accumulate with age and, in some instances, can provide a competitive advantage to the mutant cell thus allowing for its clonal expansion, a phenomenon known as clonal hematopoiesis of indeterminate potential d genomic instability in leukocytes. The observed genomic instability during and after flight suggests that the ionizing radiation (IR) exposure caused DNA damage to hematopoietic stem cells that replenish blood cells throughout life. In our recent study, we used tively, somatic mutations in CHIP-driver genes. We identified 34 nonsynonymous SNVs in 17 known CHIP-driver genes, of which TP53 and DNMT3A were the most frequent. It is conceivable that these genetic alterations may be particularly magnified when traveling

Human Research Program/HRP-funded mouse-lifetime studies to evaluate the effects of space-type and gamma IR on cardiovascular disease (CVD) development, 3-month-old male C57BL6/J mice were systematically examined for tumor development over 22 months s effects on the left and right ventricular structure and function. Moreover, in γ- and simGCRsim-IR mice, detectable neoplasms of internal organs (liver, spleen, lungs, lymph nodes) were observed at 16- and 22 months post-IR, but only one mouse developed a lymphoma solid cancers) and CVD, We performed mouse whole-exome sequencing (mWES) of white blood cells and paired tumor tissues to assess somatic mutations on a focused cohort of WT mice that develop liver tumors. Somatic variants were called with a variant allele

none in no-IR and WD-fed groups, suggesting this could be an IR-specific mutational signature. In addition, there was an age-associated increase in frameshift deletions (3%) that was increased (to 5%) in simGCRsim-IR mice, suggesting that frameshift deletions are nice showed an additional increase (10%) in stop-gain mutation, suggesting that these types of mutations are common for aging and increased by WD. Among all treatment conditions, several genes with identified mutations were associated with various cancers was specific for both types of IR, and histiocytic sarcoma only for space-type IR. Interestingly, hemangiosarcoma was found in WD-fed and γ-IR mice but not in simGCRsim-IR mice. Common signaling pathways that were affected by aging (no-IR) or exposure to either dies are underway to study mWES in paired tumor samples and to perform spatial transcriptomics assay (Visium) using adjacent tumor section of the paired tumor samples.

space travel-related stresses may lead to IR-specific and gene-specific accelerations of clonal hematopoiesis. Our studies identified specific somatic mutations in known CHIP "driver" genes during the lifetime of mice that could provide a framework for the identification missions. In addition, our studies provided scientific evidence, in animal models, on whether the CHIP-related mutant clone expansions may be the shared underlying biology for space IR-associated cancer and CVD development.

xposure"

ing IR, is a primary risk associated with deep-space missions. There are limited animal and human studies on the risk of cardiovascular disease (CVD) development due to space-IR. Our longitudinal studies in male mice showed a reduction in global systolic function in to gamma (γ) and simplified GCR simulated (simGCRsim)-IR. No significant changes were observed between the control and all other remaining IR groups over the next up to 400 days of the follow-up post-IR. At 22 months, both WT and ApoE null γ-IR male mice sized similar alterations in CV function in female ApoE and WT mice following the same IR exposure.

n (25 and 50 cGy, 500 MeV/n). Control ApoE null and WT mice were fed with mouse chow (normal diet-ND) and Western diet (WD) without irradiation. ApoE null mice are predisposed to atherosclerosis development when fed a WD mouse chow due to impaired ar (LV) function by transthoracic echocardiography at 14, 28, 365, 440, and 580 days post-IR following the same cohort of mice for each treatment condition longitudinally.

left ventricular fractional shortening (LVFS), which paired with decreased posterior wall thickness (LVPWd) may suggest an early but mild effect of IR on systolic function. By 180-, 365-, 440-, and 580 days post-IR, no alteration in LVEF or LVFS was observed in non-IR minimally reduced in 50 cGy simCRsim-IR mice at 365 days suggesting possible compensation of the altered diastolic function. In female ApoE null mice, there was no significant alteration in global LV systolic function across any treatment groups at 28-, 180-, 365-,

global systolic function or structural cardiac alterations in both female WT and ApoE null mice across any treatment group. Compared to our findings in similarly treated male mice cohort the female cohort studies showed substantially decreased in sex-specific CVD risks D risks at lower than 25 and 50 cGy simGCGsim doses of space-type IR and/or when combined with other space travel-associated stressors.

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